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Treatment of Behavioural and Psychological Symptoms in Dementia

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Contents:

Abstract	3
Introduction	3
Methods	4
Dementia	5
Diagnostic evaluation.....	5
Alzheimer's disease.....	7
Vascular dementia.....	8
Dementia with Lewy bodies.....	9
Frontotemporal dementia.....	9
Behavioural and Psychological Symptoms of Dementia.....	10
What causes BPSD?.....	10
Assessing BPS.....	11
Treatment of BPSD.....	12
Nonpharmacologic interventions.....	12
Pharmacologic treatment.....	13
Cognitive Enhancers.....	13
Antipsychotics.....	14
Antidepressants.....	15
Anticonvulsants.....	15
Benzodiazepines.....	16
Other Pharmacologic Treatments.....	17
Treatment of BPSD; Norwegian recommendation	17
Conclusions and discussion.....	18
References.....	20

Abstract

Noncognitive symptoms in dementia include many kinds of behavioural and psychological symptoms. Behavioural and psychological symptoms of dementia, BPSD, is quite common problem among individuals with dementia, and often difficult to manage. BPSD can lead to premature institutionalization and decreased quality of life for both the caregiver and the patient. The purpose of this paper is to review and describe the main characteristics of dementia and to get an overall view of the management and treatment of the behavioural and psychological problems in dementia.

There is consensus about that the nonpharmacologic interventions should allways be tried first before starting any medication for BPSD. However, it is exactly the efficacy of nonpharmacologic interventions that lack the the scientific proof in long term; more controlled trials are needed. Pharmacotherapies are used frequently to treat BPSD. Pharmacologic interventions are necessary when nonpharmacologic strategies fail to reduce behavioral symptoms sufficiently. For the time being pharmacologic treatment includes the use of cognitive enhancers, antipsychotics, antidepressants, anticonvulsants, benzodiazepines. Because of the many possible adverse effects, the medication should be chosen individually and with great care. There are still open questions and uncertainties when it comes to the safety issues of using these pharmacotherapies in patients with dementia, specially the recent warnings of increase in cardiovascular events related atypical antipsychotics need to be more closely investigated.

Introduction

Dementia is a progressive brain disorder, neurological disease that causes cognitive impairment and is often associated with aging. It affects 5 to 8 percent of people over age 65 and nearly 50 percent over age 85 (1). The incidence doubles every five years after the age of 60 years (2). In Norway over 60 000 people suffer from dementia (3). The incidence and prevalence of dementia is increasing due to longer life expectancy of the world population.

In the long term this progressive cognitive impairment causes significant physical, social and psychiatric disability. It results in a restriction of daily activities, in most cases it leads to the need for care, and causes also significant problems, burden and distress in care givers (4).

Non-cognitive symptoms are often present in dementia and play an important part for patients and caregivers. Multiple studies have shown that BPSD affects the quality of life and is a major stress factor, both for the patient with dementia and for the caregiver. Behavioral and psychological symptoms of dementia are associated with earlier institutionalization (5,6). BPSD are varied in relation to the stage of the dementia and to the aetiology, managing BPSD is an important challenge. Management and treatment of BPSD include both non-pharmacologic and pharmacologic interventions.

By getting better in recognition and management of BPSD is one way to affect positively on the quality of life of the patients and their carers, and potentially delay the transition from home to an institution. The purpose with this paper is to review some of the recent literature and to provide a summary of BPSD and of the means and medication available for managing and treating these behavioural disturbances.

The central questions are:

What is dementia?

What is BPSD; symptoms, causes, assessment of these behavioural problems?

How can BPSD be managed and treated?

Methods

Medline, PubMed and Cochrane library were searched using keywords: dementia, behaviour symptom, disorder, BPSD, treatment. The search was limited mainly to meta-analysis, reviews and guidelines starting from year 2000. Electronic database search was supplemented with hand searches of reference lists and authors.

Dementia

Decline in cognitive function is central in dementia. It is caused by pathology or damage in areas of brain that take care of processing of information; hippocampus, thalamus, temporal areas. Even minor damage in these areas can cause dementia, but also larger impairments in other parts of the brain can lead to dementia (3).

Dementia can be divided in three main groups by it's cause: I) primary degenerative dementia II)vascular dementia III) secondary dementia (3):

I Primary degenerative dementia	II Vascular dementia	III Secondary dementia
<ul style="list-style-type: none"> -Alzheimer disease -Frontotemporal dementia -Huntington disease -Parkinson disease -Lewy body dementia -other more rare degenerative diseases 	<ul style="list-style-type: none"> -small vessel disease; lacunar state, Biswanger's disease -since infarct, multiple infarcts -hypoxic dementia -other vascular diseases and dementia -mixed dementia; vascular and Alzheimer disease 	<ul style="list-style-type: none"> -alcohol /alcoholism -vitamine deficiencies (vit-B) -infections of brain structures; encephalitis, HIV/AIDS, syphilis, herpes, borrelia -Creutzfeldt-Jacob Disease (CJD) -brain tumors -head injury -hematoma -normal pressure hydrocephalus -toxic exposure, metabolic and hormonal disorders

After excluding other reversible causes of cognitive impairment, there are four dementia syndromes which are most common and account for about 90% of all cases. These are Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), and fronto-temporal dementia (FTD). These four common diseases have different clinical characteristics, and there are diagnostic criteria for each of them. It is important to distinguish between the different forms of dementia because they require different approaches, treatment and management, and because some of the risk factors can be preventable (2,3,7,8,9).

Diagnostic evaluation

Taking *medical history* is central when diagnosing dementia; it should include the cognitive domains affected, the mode of onset, the pattern of progression and the impact on activities of daily living. Also family history, past medical history, educational history and current co-morbidities are important, and the clinical history should be supplemented by an independent informant when available (2,4).

Dementia can be accompanied by different kinds of behavioural and psychological symptoms. *Assesment of behavioural and psychological symptoms of dementia* is essential both for diagnosis and management, symptoms should be actively asked about from the patient and carer (2,4).

Diagnostic Criteria for Research for the ICD-10 Dementia (10).

G 1 Evidence of each of the following

G 1.1 A decline in memory, mild, moderate, severe

G 1.2 A decline in other cognitive abilities (judgment, thinking, planning, organizing), mild, moderate, severe

G 2 Awareness of the environment (i.e., absence of clouding of consciousness)

G 3 Decline in emotional control or motivation or social behavior. At least one of the following symptoms should be present:

G 3.1 emotional lability

G 3.2 irritability

G3.3 apathy

G 3.4 coarsening of social behavior

G 4 Symptoms in Criterion G1 should have been present for at least **6** months

General neurological and psysical examination should be performed on all patients.

Laboratory screening with blood test should include complete blood cell count, Hb, sedimentation test, electrolytes, calcium, glucose, renal and liver function tests, thyreoidea and parathyreoidea function tests. Supplementary test are often required after individual consideration e.g. vitamin-B12 and serological tests for syphilis, borrelia, HIV (2,3,4).

Cognitive assesment should include a global cognitive measure (Mini-Mental State Examination) and can also include more detailed testing of memory, executive functions and instrumental functions (2).

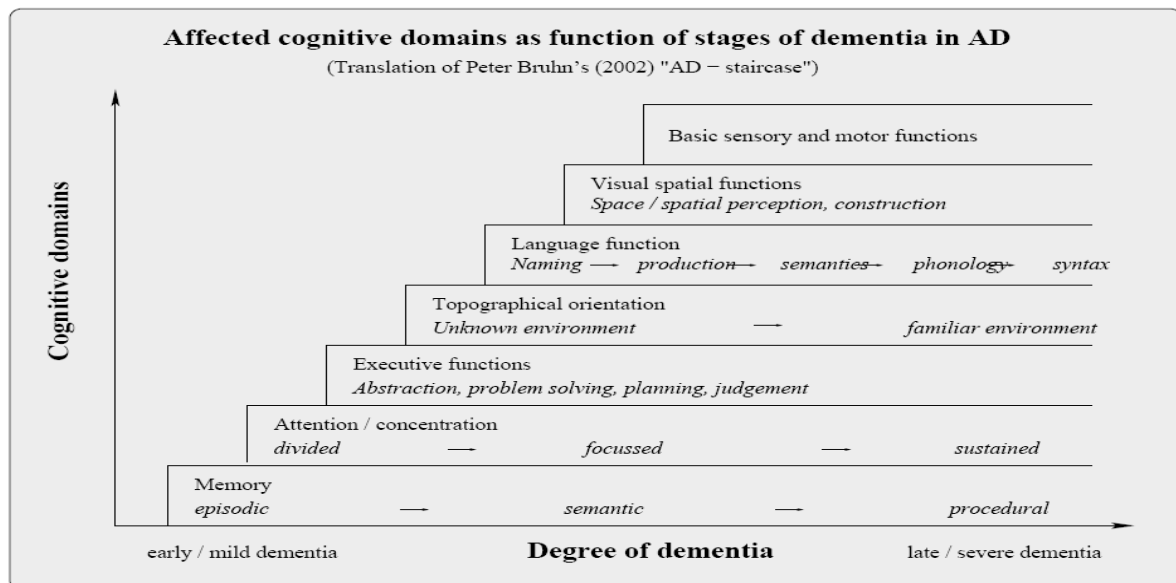
It is recommended to use structural *neuroimaging* in evaluation of every patient suspected of dementia. For example surgically treatable lesions and vascular disease can be identified by CT, to increase specificity MRI should be used. SPECT can be useful supplement when diagnostic uncertainty remains, for example in diffenrential diagnosis between AD and FTD (3,4).

Electroencephalography (EEG) may be useful adjunct but is seldom used in clinical practise. It should be used when suspecting CJD or transient epileptic amnesia. *CSF analysis* is recommended in patients with a clinical suspicion of certain diseases and atypical clinical presentations. In diagnostic doubt CSF total tau, phospo-tau and Ab42 can be helpful. With family history of an autosomal dominant dementia *genetic testing* can be useful. ApoE genotyping is not recommended (2,3,4).

Alzheimer's disease

AD is the most common cause of dementia (60%) among older adults. The major pathogenesis is the production and accumulation of beta-amyloid peptide, the formation of neurofibrillary tangles of tau protein, oxidation and lipid peroxidation, glutaminergic excitotoxicity, inflammation, and activation of the cascade of apoptotic cell death. These lead to neuron degeneration and synaptic loss. There are reduced number of cholinergic neurons in late AD; acetylcholine (ACh) is an important neurotransmitter in memory formation and loss of ACh activity correlates with the severity of AD (7, 9).

AD can be seen as 2 types of disease when it comes to debut; one with early debut before 65 years of age (with more rapid progression), and the other type with late debut after 65 years. The natural course of AD averages 10 years. Typical for AD is insidious and slow onset, progressive course, and early memory loss. At least one other cognitive impairment such as apraxia, agnosia, language dysfunction, visuospatial disorder, as well as executive dysfunction, must be seen. These defects should make up a decline from the previous level of cognitive functioning, interfering with daily activities (7, 9,10).



Memory decline in AD is characterized as a storage deficit; material cannot be recalled with cue. Memory impairment for recent events is common whereas long-term memory remains intact in the early stage, but as AD progresses the patient is increasingly unable to recall more distant memories. The motor signs are absent early in the course, as are sensory abnormalities, seizures, and gait difficulties too. Behavioural changes, including depression, anxiety, apathy, aggression, agitation, wandering, vocalization, disinhibition, and abnormal eating, are common thereafter and cause caregiver stress as well as greater use of health care service. Neuroimaging with MRI shows atrophy specially in the hippocampus and temporal-lobe area (4,9).

Cholinesterase inhibitors (ChEIs) enhance neuronal transmission by increasing the availability of acetylcholine at the receptors. This effect can provide temporary stabilization of cognition or reduction in the rate of cognitive decline, and improvement of symptoms of AD (4,9,11,12). Memantin, N-methyl-D-aspartate (NMDA) receptor antagonist targets the neurotransmitter glutamate, a chemical messenger in the brain that is involved in normal memory and learning processes. leading to symptomatic benefits in cognition, behavior, activities of daily living, and overall performance for patients (4,9,12).

Vascular dementia

Vascular dementia (VaD) counts for 20-25 % of dementias (13). There are several clinical syndromes of vascular dementia. These are categorized into single strategic infarct (single brain infarct damaging functionally critical areas), multi-infarct dementia, lacunar state, Binswanger's disease, genetic forms (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]) and hypoxic ischemic encephalopathy. Mechanisms behind these clinical syndromes can be e.g. hemorrhage, ischemia/thrombosis, vasospasm, low perfusion, hematologic and rheological problems (8).

Patients may have different clinical presentations due to difference in etiology and mechanism, for example the onset can be abrupt or insidious, the progression stepwise, fluctuating, or with continuous worsening (13). However, with atherosclerotic comorbidities as diabetes mellitus, hypertension, coronary heart disease, typical cases of VaD are often seen; The onset of cognitive decline is either subtle or abrupt with psychomotor slowing, executive dysfunction, focal cognitive deficits and motor signs. By neuroimaging the patient must demonstrate some form of cerebrovascular pathology: vascular lesions that may differ in size depending on the degree of vascular insult, lesions range from a single lacunar stroke to multiple cortico-subcortical strokes and periventricular white matter ischemia. Age is the most significant risk factor for any dementia; but other factors associated with health status earlier in life may predispose to developing VaD. For example, atherosclerotic risk factors such as smoking, hypertension, myocardial infarctions, hyperlipidemia, and diabetes mellitus predispose older adults to cerebrovascular disease (CVD), and this can cause VaD (8).

There is no specific medication for VaD but treating involves use of medications and addressing the factors behind the cardiovascular disease (8). However, ChEIs may be considered with mild to moderate severity of VaD; evidence indicates that (donepezil) ChEIs can improve cognitive symptoms and functional ability and is well tolerated (14,4). Cholinergic deficits in VaD are due to ischemia of basal forebrain nuclei and of cholinergic pathways (14).

Dementia with Lewy bodies

10-15% of the patients with demens have DLB. It is a syndrome caused by abnormal microscopic deposits of protein (ubiquitin, alpha-synuclein), neuronal inclusion bodies called Lewy bodies, which destroy nerve cells. Neurochemically there is a reduction of neurotransmitter ACh and dopamin. Lewy bodies can cause symptoms typical of Parkinson disease, such as tremor, rigidity and bradykinesia, as well as dementia similar to that of Alzheimer disease. Lewy body dementia affects thinking, attention, and concentration more than memory and language. The criteria for diagnosis of DLB are highly specific but not sensitive; core clinical features are fluctuating cognitive impairment, visual hallucinations, and parkinsonism (15,16). Its other features are repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematized delusion, hallucination of other modalities, REM sleep behaviour disorder, and depression. When making a diagnosis, the two most confusing diseases are DLB and Parkinson's disease with dementia (PDD) because the clinical features are so similar. If the onset of dementia is within 12 months of parkinsonism's onset, it is likely to be DLB. By contrast, if the onset of parkinsonism is more than 12 months earlier than dementia onset, it should be PDD. Patients with PDD have parkinsonian features at the time of dementia diagnosis, whereas only 25-50% of those with DLB have parkinsonism at the time of diagnosis. Patients with DLB usually have extrapyramidal signs as postural instability and masked face, whereas tremor is less prominent than among those with PDD (16).

Rivastigmine may decrease some psychiatric symptoms associated with DLB, patients with DLB treated with cholinesterase inhibitors show improvement in cognition and neuropsychiatric symptoms (4). Levodopa/carbidopa may improve motor function in some patients with DLB; however, in many patients this combination has no effect and may exacerbate psychiatric symptoms or confusion. Selective serotonin reuptake inhibitors are the drugs of choice in depression. Antipsychotics should not be used for DLB patients (10,15,16).

Frontotemporal dementia

The clinical picture of frontotemporal dementia (FTD) is caused by degenerative disease affecting the frontal and temporal lobes, and is described with the emphasis on prominent personality and behavioural changes with less prominent memory loss early in the course. The clinical onset is insidious and usually between 35-70 years of age. FTD is often misdiagnosed as personality disorders or late-onset psychiatric disorders. Behavioural and emotional changes are always present as e.g. disinhibition, impulsivity, distractibility, loss of personal awareness, antisocial behaviour, hyperorality (e.g., excessive eating), social withdrawal, stereotyped or preservative behaviour, and speech output change (e.g., reduction / stereotype / echolalia). 50% of patients have a family history of dementia in a first-degree relative. There are three principal clinical subtypes of FTD: a behavioral/dysexecutive (frontal) variant and 2 variants with prominent language impairments. There are currently no approved medications indicated for the treatment of frontotemporal dementia (4,17).

Behavioral and Psychological Symptoms of Dementia

Behavioral symptoms in dementia are quite common and often much more troubling than for example amnesic symptoms. These symptoms may even start before diagnosis of dementia is made (18). It is estimated that about 90% of patients with dementia will develop behaviour problems at some point during the illness. These symptoms include e.g. agitation, aggression, delusions, hallucinations, and wandering, also depression and sleep disturbances can also occur with dementia. The prevalence of BPSD increases with disease severity. The presence of these symptoms leads to greater functional impairment in patients with dementia. Disruptive behaviour, specially agitation and aggression commonly precipitate institutional placement. Intervention is important because BPSD can respond to treatment more readily than cognitive and functional deficits do, and effective treatment can delay institutionalization. (6,12).

Delusions
Agitation/aggression
 -Verbal
 -Physical
Hallucinations
 -Auditory
 -Visual
Misidentifications
Depression
Anxiety
Euphoria/disinhibition
Apathy
Irritability
Aberrant motor behaviors
 -Pacing
 -Wandering
 Restlessness
Nighttime behaviors (e.g., sundowning)
Appetite/eating changes

Table: BPSD

What causes BPSD?

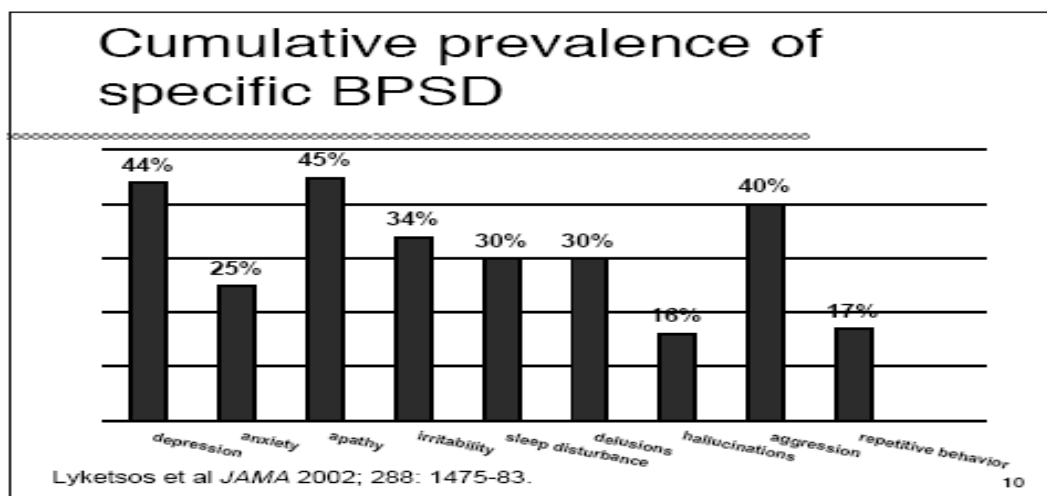
The most important cause for BPSD is the illness itself and it's severity, the neurobiological changes go hand in hand with the progression of these symptoms. In AD the psychological symptoms as depression and anxiety are more common in the early phase of the disease and behavioral problems in more advanced stage. In Changes in levels of the neurotransmitters in the CNS have relation to spesific types of BPSD. Local loss of neurons in the brain and the formation of neurofibrillary tangles for example, are related to apathy and psychotic behaviour (19). Other possible reasons behind the BPSD are misinterpretation (inviroment, caregiver, signals/cues), pain (bone, dental, skin breakdown,

rash), fear, fatigue, boredom, over/understimulating and communication difficulties. Also delirium increases confusion. One important cause for aggression towards caregivers can be intimate care (toileting, bathing). Symptoms are often triggered by unmet needs and lack of understanding of the patient (20).

Assessing BPSD

It is not always that behavioral problems have to be treated in patients with dementia. The need for treatment is related to the type and severity of the symptoms, and has to be evaluated individually. Assessing BPSD should begin with a few simple questions as: What exactly is the problem? Why is it a problem now; is it a new problem, is there something new, changes in routines or environment? Whose problem is this; is it patient, visitors, family, caregivers, the staff, other residents that are concerned about or suffer because of the behaviour? Is there a safety risk either to the individual or someone else?

When assessing BPSD one should try to identify the reasons behind the problems, central in this is to interview both the patient and the caregivers. Laboratory screening and thorough physical examination of the individual with dementia is an important part of assessment, this to rule out medical conditions and sensory deficits, identify co-morbidity and adverse effects of medication that could cause the behavioural disturbances. There should be evaluation for conditions as pain, constipation, delirium, unmet needs and physical involvement. The possibility of depression should not be forgotten, it is common in older adults including individuals with AD, and is often untreated. There are many kind of neuropsychiatric symptom rating scales that can be used as help in assessment e.g. Neuropsychiatric inventory (NPI), Behave AD, Geriatric Depression scale (GDS), Cohen-Mansfield Agitation Inventory (11,19,21).



Treatment of BPSD

The management of BPSD requires a comprehensive, multimodal approach that begins with assessment and diagnosis. Untreated BPSD can contribute to premature institutionalization, increased financial cost, decreased quality of life for both the caregiver and the patient, significant caregiver stress, stress to nursing staff, and excess disability of the individual with dementia. Treatment and management of BPSD consists of two main measures, which are nonpharmacologic interventions and pharmacologic treatments (11,22).

Nonpharmacologic interventions

The nonpharmacological interventions should be tried first before drugs are used. Environmental manipulations can be crucially important. Caregivers can be taught strategies to reduce behavioral disturbances in patients with dementia. Use of validation therapy or reminiscence therapy and the use of therapeutic activities may bring positive effect (4,11,23,24). Nonpharmacologic interventions that can be tried by caregivers and staff e.g. in individuals with BPSD are (4,11):

Nonpharmacologic interventions for reducing behavioral disturbances

Provide the patient with a predictable routine (exercise, meals, and bedtime should be routine and punctual).

Allow the patient to dress in his or her own clothing and keep possessions.

Before performing all procedures and activities, explain them to the patient in simple language.

Simplify all tasks; break complex tasks into steps and provide instructions for each step.

Use distraction and redirection of activities to divert the patient from problematic situations.

Ensure that comorbid conditions are optimally treated.

Provide a safe environment (no sharp-edged furniture, no slippery floors or throw rugs, no obtrusive electric cords).

Equip doors and gates with safety locks.

Install grab bars by the toilet and in the shower.

Use calendars, clocks, labels, and newspapers for orientation to time.

Use color-coded or graphic labels (on closets, table service, drawers) as cues for orientation in the home environment.

Use lighting to reduce confusion and restlessness at night.

Avoid glare from windows and mirrors, noise from a television, and household clutter.

Reduce excess stimulation and outings to crowded places (overexposure to environmental stimuli can lead to agitation and disorientation).

Consider using a day care program for patients with dementia.

Nonpharmacologic interventions for behaviour problems in AD may enable a reduction in the dosage, duration or complexity of required medication(14). For the reduction of neuropsychiatric symptoms, behavioral management techniques centered on individual patients' behavior have shown to be successful (23). Numerous behavioral and psychosocial interventions have been tried, for example conditioning, pet therapy, learning experience, music/stimulation therapy, aroma therapy. In some studies these show positive effect with behaviour modification, but often these have no long term effect. More studies are required to determine the effectiveness of these various therapies (20,22,23,25).

Pharmacologic treatment

There is evidence that pharmacotherapies are used frequently to treat BPSD, even when recommendations suggest the use of nonpharmacologic therapies first. Pharmacologic interventions are necessary when nonpharmacologic strategies fail to reduce behavioral symptoms sufficiently. As pharmacologic treatment it has been tried the use of cognitive enhancers, antipsychotics, antidepressants, anticonvulsants, benzodiazepines (11,22).

The psychotropic agent should be initiated in a lowest possible dosage that should be increased slowly, the patient should be monitored for side effects. Until adequate response occurs or side effects emerge, the dosage should be increased. Also potential drug interactions should be kept in mind. The dosage of psychotropic agent should be reduced after behavioral disturbances have been controlled for four to six months; this to determine whether continued pharmacotherapy is required (22).

The choice of psychopharmacologic agent is dictated by specific target symptoms. Some behaviors, such as wandering and pacing, frequent repetition, are not amenable to drug therapy. Apathy, depression, anxiety, hallucinations, delusions, agitation, and aggression are target symptoms that are more likely to respond to pharmacotherapy. Pharmacotherapy could be considered a first-line therapy in the context of severe depressive symptoms, psychosis, and aggression, which place the patient or others at risk of harm (11,22).

Cognitive Enhancers

The cognitive enhancers are the cholinesterase inhibitors (ChEIs) donepezil, galantamine, and rivastigmine, and the NMDA receptor antagonist memantine. There is increasing evidence that these agents have beneficial effects also on behaviour; Cholinesterase inhibitors may improve BPSD, this mainly in mild and non-psychotic behaviour disorders. Use of a psychotropic agent may be necessary, if behavioral disturbances continue to exist despite cholinesterase inhibitor therapy. There is a risk of adverse effects when using ChEIs, including nausea, vomiting, diarrhea. Memantine is reported to be better tolerated (11,21,22,26).

Antipsychotics

The antipsychotics are the best-studied pharmacologic interventions for BPSD; several systematic reviews have concluded that the evidence for their efficacy is better than that for any other drug class. Antipsychotics are among the medications most commonly used to treat BPSD. Agitation, aggression, psychosis, and sleep disturbance are the symptoms most likely to respond to antipsychotics. But especially in residential and nursing homes overprescribing has however become a problem; up to 40% of people with dementia may be taking antipsychotics, often inappropriately and with little monitoring. This is problematic specially because of the adverse effects as increased risk of falls and drowsines, parkinsonism, akathisia, tardive dyskinesia (6,21,22,25).

Metaanalyses of *typical antipsychotics* such as haloperidol suggest significant benefit, however, the side effects limit the use of haloperidol. It can be associated with severe effects involving the cholinerg, cardiovascular, and extrapyramidal system. It is likely owing to the fact that dementia patients are at significant risk for developing for example extrapyramidal symptoms such as parkinsonism and tardive dyskinesia, that typical antipsychotic use has declined. Typical antipsychotics should be second line therapy, mainly for patients who don't tolerate or respond on atypical antipsychotics (11,21,22,24).

There have been several large, well-designed, placebocontrolled trials of *atypical antipsychotics*, also called second-generation antipsychotics. These include risperidone, olanzapine, quetiapine, and aripiprazole. Atypical antipsychotics are typically licensed for the treatment of schizophrenia, acute psychosis and other mental disorders such as bipolar disorder. The off-label use of these agents in the control of non-schizophrenia psychosis or non-psychotic behavioural problems has become more common and these agents have been widely used to treat the BPSD. They are usually better tolerated than the typical neuroleptics. (11,20,24,27)

Some systematic reviews and metaanalyses have questioned the efficacy of the atypicals, but more often it is suggested significant benefits greater than placebo; this especially and mainly for risperidone (significant in aggression and psychotic symtoms) and in some extension for olanzapine (benefit in aggression and anxiety) (6). An average dosage of 1 mg risperidone daily is significantly more effective than placebo and as effective as haloperidol, but the advantage is that it is less likely to cause extrapyramidal symptoms than haloperidol. Olanzapine with dosage of 5 to 10 mg daily has also shown to be significantly more effective than placebo. Olanzapine use is associated with sedation and incoordination at all doses (6,12,27).

Recent findings from randomised, controlled clinical trials have cast new doubt on the safety of atypical antipsychotics in treating BPSD; it was reported findings in meta-analysis on overall mortality and it was given warning of an increased risk of cardiovascular events, CVAEs (stroke, TIA, cerebral ischaemia), the first time was in 2002. The warning was at the beginning given about an increased risk of CVAEs in dementia patients treated with risperidone, but later, the following years, similar

warnings have been released for olanzapine and subsequently for all the available atypical antipsychotics. However, observational studies offer compelling data that typical antipsychotics are as likely to be associated with increased risks of CVAEs and mortality, when compared with the atypical antipsychotics, and there hasn't been significant difference. The increased risk for death and CVAEs could only be seen when atypical antipsychotics were combined in a meta-analysis (15). According to the best available evidence at the time being, can atypical antipsychotics still be used for severe agitation, aggression, and psychosis. Individual patient characteristics, benefits of the therapy and risk factors should first be considered. More studies are required in the future to clear out risk of CVAEs (1, 22,27,28,29).

There are a few randomized controlled trials about the behavioral impact of discontinuation of antipsychotic use in people with dementia in the long-term care institutions. The result of these studies indicate that the antipsychotic discontinuation is likely to be safe intervention and usually don't cause significant worsening of behavior. Thereby there does not seem to be any obvious need for long-term treatment. However it is important to take into account the baseline dose; patients with high dose on antipsychotic drug at baseline have greater likelihood of exacerbation of behavioral symptoms and thereby need close monitoring. Patients who were using relatively low doses of antipsychotics were more likely to remain stable or even improve after drug discontinuation (30,31). Also patients with lower baseline score in Neuropsychiatric Inventory (NPI) Questionnaire seem to be less likely to develop marked behavioral problems when stopping antipsychotic drug therapy (31, 32).

Antidepressants

In AD patients depressive symptoms are common, and antidepressants have been studied both for the treatment of depression and other BPSD as agitation and aggression. There have been several RCTs of antidepressants; tricyclics, SSRIs and other antidepressants. Antidepressants were significantly better than placebo in treatment of depression. Several RCTs have examined antidepressants used to treat agitation. Tricyclics are not recommended because of the higher risk for side effects, SSRIs are relatively well tolerated. In some studies only citalopram have shown to be significantly better than placebo, and its use was in some degree associated with improvements in agitation, aggression, and psychosis (20, 21).

Reasonably good data have indicated that antidepressants, especially the SSRIs, are safe and effective for the treatment of depression in AD, but more data are required to determine the efficacy for the treatment of agitation and other BPSD (20, 21).

Anticonvulsants

Selective anticonvulsants have been used to treat patient with dementia, mainly when psychotic behavior results in aggression and agitation. RCTs have studied carbamazepine and valproate

treatment. Carbamazepine seems to have significant benefits for agitation and aggression, but there is relatively high risk for drug-drug interactions and side effects. Also its therapeutic window is quite narrow (9,12).

It was earlier hoped that the use of valproate would represent a safer and better-tolerated alternative than carbamazepine. Even if in some studies it has shown benefit versus placebo, in many RCTs the results were all negative. Of greater concern is the tolerability of valproate found in studies; use of valproate has shown high rates of adverse events, e.g. thrombocytopenia, whereas lower dosages of valproate were ineffective, higher dosages were associated with an unacceptable rate of adverse events. Other anticonvulsants (gabapentin, topiramate, lamotrigine) have been examined for BPSD, the evidence is still insufficient for recommendations (22).

Benzodiazepines

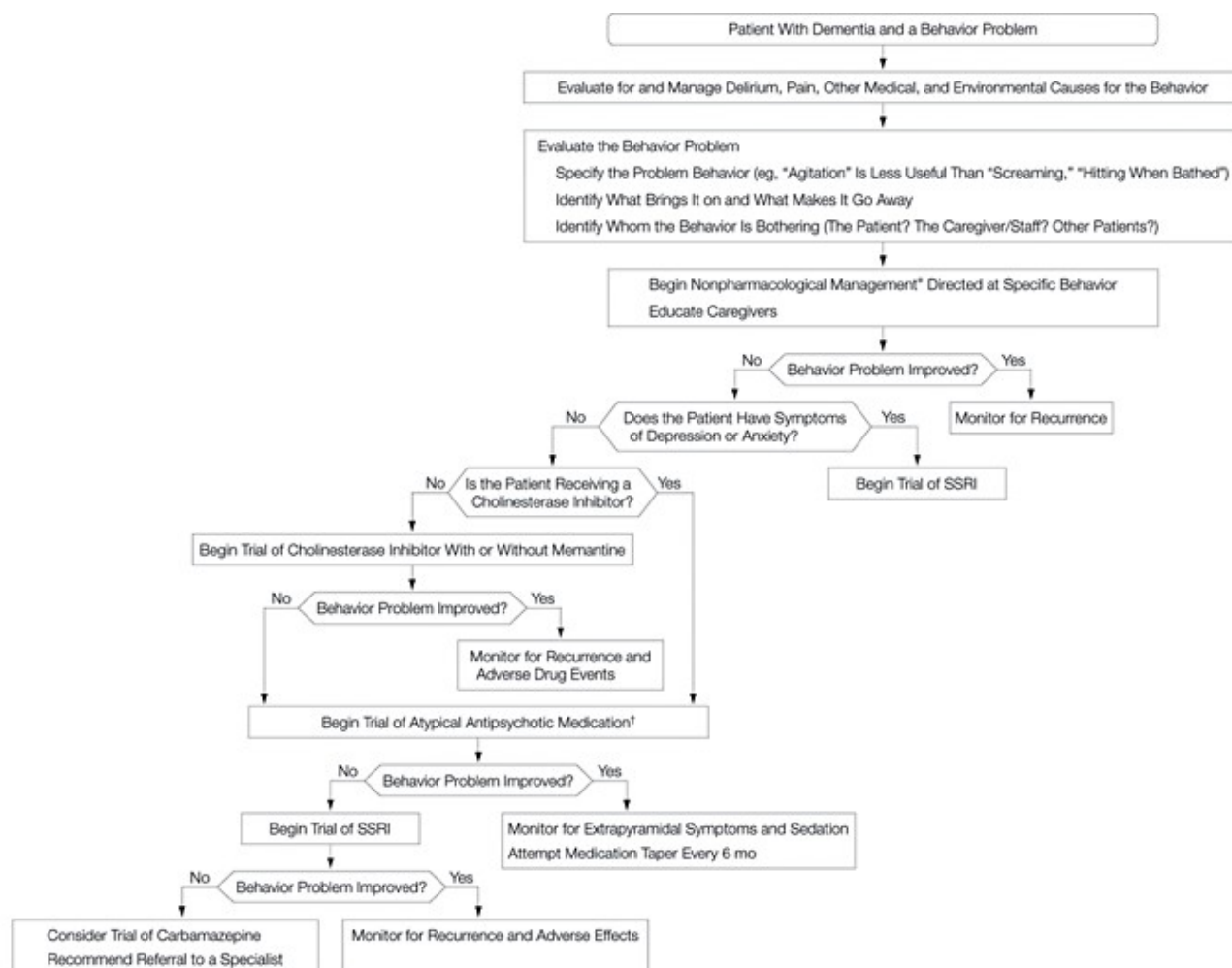
Several studies have been made about benzodiazepines, including oxazepam, diazepam, alprazolam, and lorazepam. Benzodiazepines cause tolerance and dependence in long-term use, and even short-term regular use in the elderly is associated with significant adverse effects as sedation, falls, and cognitive impairment. Guidelines tend to relegate their use to "as-needed/emergency" use only. Evidence for the use of benzodiazepines in these circumstances is provided by comparing intramuscular olanzapine and lorazepam with placebo for the management of acute agitation in patients with dementia. Both medications were significantly more effective than placebo, with no differences in adverse events (11,22,24).

Other Pharmacologic Treatments

There has been proposed noradrenergic mechanisms for BPSD and thereby the beta blockers propranolol and pindolol have been studied for agitation and aggression. Studies have shown either limited effect or benefits that appear to diminish over time. Use of beta blockers in frail elderly is also limited by contraindications because of the potential for adverse events as hypotension and bradycardia (22).

Also various other pharmacologic approaches for BPSD have been studied. These studies have included buspirone, a nonbenzodiazepine serotonergic anxiolytic, preparations of estrogen, dronabinol for anorexia in dementia and melatonin for sleep disturbances in patients with AD. The results have either been negative or insufficient to allow conclusions about the effects or safety (22).

Figure. Recommended Algorithm for Management of Neuropsychiatric Symptoms of Dementia (21).



SSRI indicates selective serotonin reuptake inhibitor.

*Music therapy, aromatherapy, pet therapy, or other approaches.

†Caution is advised in patients with dementia with Lewy bodies.

Norwegian recommendations for treatment of BPSD

There is consensus with the overall international recommendations about assessment of BPSD, and about the importance of nonpharmacologic interventions being the primary choice in managing the behavioral symptoms. Pharmacologic treatment may be initiated if no results are gained with nonpharmacologic means, and the medication should be chosen by the target symptoms and after careful individual evaluation of the patient (33).

Antipsychotics should only be used if severe behaviour disorders with aggression, agitation or psychotic symptoms, then risperidone should be the first choice. Use of older antipsychotics is not recommended, except in rare cases haloperidol may carefully be tried. In DLP antipsychotics are contraindicated (33).

Initial dosage recommended for risperidone is 0,25 mg 1x2 daily, can be adjusted individually up to 0,5 mg 1x2; the latter is described to be the optimal dosage for most of the patients. Some patients may need even higher dosage (1mgx2). Observation of effect and adverse effects is needed continually. If no effect is seen after 4-6 weeks from initiation of risperidone, the treatment should not be continued with. The dosage of psychotropic agent should be reduced after behavioral disturbances have been controlled 3 months (33).

SSRI is the first-line choice for patients with fear, anxiety or depression, which can be seen as irritability or aggression. Cholinesterase inhibitors should be the first-line choice in any type of dementia when visual hallucinations, and also for other behaviour symptoms in patients with DLP. Anticonvulsants carbamazepine and valproate can be tried if severe aggression and agitation, in cases where there is no response for other recommended pharmacotherapies (33).

Conclusions and discussion

Behavioral and psychological symptoms are fairly common among individuals with dementia, and benefit from considered therapeutic interventions. Intervention effective on one symptom may not be effective for another. The nonpharmacologic interventions should always be the first choice.

Both medication and nonpharmacologic interventions reduce severity of the symptoms but rarely eliminate the target behavior. In treating dementia patients with severe and complex symptoms psychotropic medication has its place. In any case, it is important to balance the benefits and risk when considering medication, all the pharmacologicals used for BPSD have adverse effects which can be dangerous and even fatal for a frail and fragile elderly patient with dementia. One central point in pharmacologic treatment is regular, continuous observation and reassessment after initiation.

The initiation of pharmacologic treatment requires individual, critical assessment. For the clinician this can be a rather difficult task in the middle of the jungle of adverse effects and the recent safety warnings for increased risk of cardiovascular events in antipsychotics. Even if the effectiveness of atypical antipsychotics is somewhat limited, they may have an important role in treatment of BPSD. More controlled trials are needed to establish efficacy of specially nonpharmacologic interventions, which should always be tried before starting with medication. But there are also still many open questions and uncertainties when it comes to effectiveness of pharmacotherapies used for BPSD in patients with dementia for the safety issues concerning atypical antipsychotics and; these need to be more closely investigated.

Pharmacologic treatments of BPSD is not meant to be a life-long treatment, but there is still a lot of antipsychotic usage in elderly dementia patients that is inappropriate; the medication is used for chronic sedation purposes, over weeks and months, and even longer. This can partly be due to the

fact that the behaviour symptoms are exhausting for the caregivers and the staff in nursing homes. The institutions may also be under staffed. And the clinicians can have inadequate knowledge and skills for treating the elderly patient with dementia. It is not only controlled trials that are needed in the future, there should also be greater investment in planning of the health care system and the care of the elderly, and in education of the caregivers and health personal in management of dementia and BPSD.

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